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Negative Pressure Wound Therapy (NPWT)

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by

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Invitation.
This document was developed to assist decision-making in the McGill University Health Centre. All are welcome to make use of it. However, to help us estimate its impact, it would be deeply appreciated if potential users could inform us whether it has influenced policy decisions in any way.
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TIMELINES

This report is an update to our TAU Report #19:

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ABBREVIATIONS

CUSM	Centre universitaire de santé McGill
HTA	Health Technology Assessment
IQWiG	Institute for Quality and Efficiency in Health Care
ITT	Intention to Treat
MUHC	McGill University Health Centre
NPWT	Negative Pressure Wound Therapy
RCT	Randomized Controlled Trial
TAU	Technology Assessment Unit
TPN	Thérapie par pression négative
VAC	Vacuum-assisted Closure

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PRINCIPAL MESSAGES

- There is now adequate evidence to conclude that NPWT accelerates healing of diabetes-associated lower extremity wounds.

- There is less convincing evidence that NPWT will accelerate healing of several other types of wounds. Evidence of its value for the treatment of pressure ulcers, necrotizing fasciitis, and wounds complicated by osteomyelitis remains conflicting.

- Currently this treatment is well established at the MUHC, with 229 patients receiving this treatment per year, with a budget impact of approximately $155,000 compared to alternative treatment.

- It is recommended that the MUHC should continue to fund this technology.

- It is recommended that the *Programme for Wound Care* should undertake an RCT to evaluate the effectiveness of NPWT for pressure ulcers, necrotizing fasciitis, and wounds complicated by osteomyelitis.

EXECUTIVE SUMMARY

Background

Traditionally, wounds that do not heal by first intention have been treated by moist saline dressings or various forms of interactive foam. Over the past decade such wounds have increasingly received Negative Pressure Wound Therapy (NPWT). This report is an update of a health technology assessment (HTA) evaluating this technology, published in 2005 by the Technology Assessment Unit (TAU) of the McGill University Health Centre (MUHC).

Method

A systematic search was carried out for evidence of the effectiveness of this technology, derived from HTAs, systematic reviews, or randomized controlled trials, published in peer reviewed journals in English or French since January 2005. An estimate was also made of the present use and cost of this technology, from the point of view of the MUHC.

Results: Literature review

Systematic reviews/HTAs: We identified seven systematic reviews, of which six were published in 2008 or 2009. Five of these concluded that the available evidence was insufficient to support the use of NPWT, while two concluded that NPWT was more effective than conventional treatments for lower limb wounds and diabetic foot ulcers. We also identified four HTA reports. All four HTA reports consistently concluded that the available evidence did not demonstrate the clinical effectiveness of NPWT therapy compared to conventional therapy.

Randomized Controlled Trials (RCTs): We identified 17 relevant RCTs that considered effectiveness, 14 that reported adverse events and six that reported costs.

Effectiveness

The different outcome measures used in different trials prevented meta analysis. Because of the nature of these trials it was necessary to create an instrument to assess their quality. We used a scale of: A=Good, B=Acceptable, C=Poor.

Diabetic foot ulcers: Seven RCTs (two quality A, three quality B, and two quality C) provided reasonably consistent evidence that NPWT resulted in more rapid healing than the control treatments used.

Mixed Wounds (chronic and acute): Four of the five studies found improved healing compared to control treatment with NPWT therapy. In two (quality B,C) this reached statistical significance, and in two (quality B, C) it did not. In one study (quality C) no difference was found in wound healing between NPWT and other therapies.

Pressure ulcers: In three studies**,** two found evidence of benefit, which was statistically significant in one (quality B). The third study (quality C), found no evidence of benefit.

Special applications

We identified two RCTs involving special applications of NPWT that were significantly different to other wound treatments. One involving use of NPWT for acute necrotising fasciitis found (statistically insignificant) evidence of benefit. Another, comparing NPWT with Polyglactin 910 mesh for closure of abdominal wounds found no evidence of benefit.

Safety

There was no evidence from the reviews or the RCTs that this technology was associated with increased complications.

Costs

Six RCTs briefly reported on the costs of NPWT, while two studies presented a full economic analysis in separate papers. Results of economic analyses varied greatly. In general, NPWT did not appear to be substantially more expensive than traditional treatment. In three studies, the overall costs of wound treatments, including hospitalization, nursing etc., were actually lower with NPWT than with control therapy , while in two studies costs were lower with control therapies.

NPWT at the MUHC

At the MUHC almost all wounds are currently treated by NPWT. In the past year 229 patients received this treatment, involving 5,803 days of hospitalization.

Costs: The average cost of NPWT at the MUHC is currently $486 per patient week. The cost (and probability bounds) of the advanced moist wound treatment that would be employed if NPWT were not available would be $299 ($238 - $357) per week. The net *budget impact* of using NPWT instead of the alternative for 829 treatment weeks is thus $155,023 ($106,941 - $205,592) per year

CONCLUSIONS

- **Although additional RCTs of substantial size are still necessary to establish the value of NPWT for certain types of wound, there is now sufficient evidence to conclude that the healing of diabetes-associated chronic lower extremity wounds can be accelerated by its use.**
- **There is less convincing evidence that the healing of several other types of wound can also be accelerated by use of NPWT.**
- **Evidence concerning the use of NPWT for the treatment of pressure ulcers, necrotising fasciitis, and wounds complicated by osteomyelitis remains conflicting.**
- **The increased cost of using NPWT at the MUHC, compared to the alternate available option is approximately $187 per patient week. Currently, 829 treatment weeks per year with NPWT costs the MUHC approximately $155,000 more than the alternative option**.

RECOMMENDATIONS

- **In view of the evidence that NPWT promotes the healing of many types of wound, and because at this time NPWT is already the accepted standard treatment used throughout the MUHC it is recommended that the MUHC should continue to fund this technology .**

- **The *Programme for Wound Care* should be encouraged to undertake an RCT to evaluate the effectiveness of NPWT and its influence on length of hospital stay and costs for the treatment of pressure ulcers, necrotising fasciitis, and wounds complicated by osteomyelitis.**

SOMMAIRE

Contexte

Traditionnellement, les plaies qui ne guérissaient pas après une première intervention étaient traitées à l'aide de pansements salins humides ou à l'aide de diverses formes de mousses interactives. Au cours de la dernière décennie, de telles plaies furent de plus en plus traitées par pression négative (Negative Pressure Wound Therapy (NPWT)). Ce rapport est une mise à jour de l'évaluation de cette technologie publiée en 2005 par l'Unité d'évaluation des technologies (TAU) du Centre universitaire de santé McGill (CUSM).

Méthodologie

Une recherche systématique pour des données probantes fut réalisée en regard de l'efficacité de cette technologie à partir d'évaluations technologiques, de revues systématiques ou d'études randomisées publiées dans les journaux révisés par les pairs, en anglais ou en français, depuis janvier 2005. Une évaluation de l'utilisation de cette thérapie et des coûts impliqués fut aussi faite au CUSM.

Résultats. Revue de la littérature

Revues systématiques – Rapports d'évaluation des technologies

Sept revues systématiques furent identifiées dont six furent publiées en 2008 ou 2009. Cinq de ces revues concluaient que les données disponibles ne supportaient pas l'utilisation de la thérapie par pression négative (TPN) tandis que deux études concluaient que la TPN était plus efficace que les traitements classiques pour les plaies aux membres inférieurs et les ulcères diabétiques du pied. Enfin, 4 rapports d'évaluation technologique (HTA) concluaient tous que les données disponibles ne démontraient pas une efficacité clinique supérieure de la TPN par rapport à la thérapie conventionnelle.

Études randomisées

Dix-sept études randomisées pertinentes considérant l'efficacité clinique furent identifiées. Parmi celles-ci, 14 études rapportaient des complications et six études s'attardaient aux coûts.

Efficacité clinique

Les données recueillies parmi ces études ne se prêtaient pas à une meta analyse. Étant donné les types différents d'essais, il fut nécessaire de développer un instrument pour évaluer la qualité de ces études. L'échelle suivante fut utilisée : A = bon, B = acceptable et C = faible.

Ulcères diabétiques du pied

Sept études randomisées (deux études de qualité A, trois de qualité B et deux de qualité C) ont toutes démontré des évidences raisonnables supportant le fait que la TPN se traduit par une guérison plus rapide, comparativement aux traitements de contrôle.

Plaies diverses (chroniques et aigues)

Quatre des cinq études identifiées ont démontré une guérison améliorée avec TPN, comparativement aux traitements de contrôle. Deux de ces études (de qualité B et C) étaient statistiquement significatives tandis que deux autres études (de qualité B et C) ne l'étaient pas. Enfin, la dernière étude (de qualité C) ne démontrait aucune différence entre la guérison par TPN et les autres traitements.

Ulcères de pression

Parmi trois études traitant des ulcères de pression, deux études ont mis en évidence un certain bénéfice de la TPN, statistiquement significatif dans une seule étude (de qualité B). Par comparaison, la troisième étude (de qualité C) n'a démontré aucun bénéfice lié à la TPN.

Applications particulières

Deux études randomisées furent identifiées impliquant la TPN pour le traitement de plaies particulières. La première étude conclut que l'utilisation de la TPN lors de fasciites nécrosantes était bénéfique (statistiquement non-significatif) tandis que la seconde ne démontra aucun bénéfice lié à la TPN par rapport à l'utilisation d'un pansement avec le Polyglactin 910 pour la fermeture des plaies abdominales.

Innocuité

Aucune évidence ne fut trouvée parmi les revues systématiques ou les études randomisées, associant la TPN à une augmentation des complications.

Coûts

Six études randomisées ont touché brièvement aux coûts de la TPN tandis que deux autres études ont présenté une analyse économique complète. Les résultats des analyses économiques variaient de façon importante. De façon générale, la TPN ne semblait pas être plus dispendieuse que le traitement classique. Dans trois études, les coûts totaux de traitement par TPN, incluant les frais d'hospitalization, les soins, etc., étaient moins élevés que ceux du traitement de contrôle, tandis que dans deux autres études, ces coûts étaient moins élevés avec le traitement de contrôle qu'avec le traitement par TPN.

La TPN au CUSM

Au CUSM, presque toutes les plaies sont traitées par TPN. Au cours de l'année précédente, 229 patients ont reçu ce traitement, impliquant 5 803 jours d'hospitalization.

Coûts

Le coût moyen du traitement par TPN au CUSM est environ 486 $ par patient pour une semaine. Par comparaison, le coût du traitement d'un patient par pansements humides dans le cas où le traitement TPN ne serait pas disponible, serait environ 299 $ (238 $ - 357 $) par semaine. L'impact budgétaire net découlant de l'utilisation de la TPN au lieu du traitement alternatif pour 829 traitements-semaine est donc de 155 023 $ (205 592 $ - 106 941 $) par année.

CONCLUSIONS

- **Il existe actuellement assez d'évidences pour conclure que la guérison des plaies chroniques des membres inférieurs associées au diabète, peut être accélérée par l'utilisation de la TPN.**
- **En se basant sur des évidences plus faibles, il est probable que la guérison de plusieurs autres types de plaies peut aussi être accélérée par la TPN.**

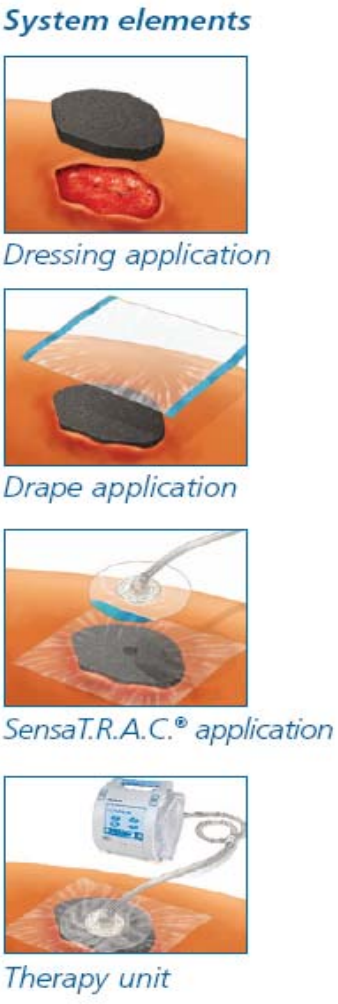
- **Les évidences supportant l'utilisation de la TPN pour le traitement des ulcères de pression, des fasciites nécrosantes et des plaies impliquant une ostéomyélite, demeurent conflictuelles.**
- **Les coûts résultant de l'utilisation de la TPN par rapport aux options disponibles sont de 486 $ et 299 $ par patient-semaine, respectivement. Actuellement, 829 traitements-semaine par année avec TPN coûtent au CUSM environ 155 000 $ de plus que les options alternatives.**

RECOMMANDATIONS

- **En prenant en considération les évidences que la TPN favorise la guérison de plusieurs types de plaies et qu'actuellement la TPN est le traitement accepté et utilisé au CUSM, il est recommandé que le CUSM continue de supporter financièrement cette technologie.**
- **Le Programme pour le soin des plaies devrait être encouragé à entreprendre une étude randomisée pour évaluer l'efficacité clinique de la TPN et son impact sur la durée d'hospitalization et des coûts lors du traitement des ulcères de pression, des fasciites nécrosantes et des plaies impliquant une ostéomyélite.**

Negative Pressure Wound Therapy (NPWT)

BACKGROUND



Traditionally, wounds that do not heal by first intention have been treated by debridement, followed by saline or wet-to-moist dressings. More recently such dressings have been increasingly replaced by moist interactive dressings such foams, calcium alginates, transparent films, hydrogels, hydrocolloids, hypertonic, hydrofiber, charcoal , antimicrobial and biological dressings.

In 2001 Negative Pressure Wound Therapy (NPWT) received approval by Health Canada, and since that time this treatment has been increasingly used [1] for the treatment of such wounds. In this approach it is believed that negative pressure drains exudate, reduces edema , draws the sides of the wound together, promotes angiogenesis and influences tissue growth by removing barriers to cell migration and proliferation , all in such a way as to accelerate healing. The procedure is carried out by placing a piece of proprietary foam over the wound, and covering it with transparent adhesive film. A negative pressure source, set between 50 -125 mmHg, then draws out exudate via a monitoring drainage tube into a disposable canister. The attached diagram is reproduced from the publicity of KCI Medical, Canada Inc (Kinetic Concepts,Inc., San Antonio, TX),

In July 2005 a TAU report [1] entitled ,“Vacuum-assisted Wound Closure Therapy” concluded, in concurrence with five cited Health Technology Assessments and one systematic review, that there was insufficient evidence to justify recommending routine use of VAC therapy. The

report recommended that "no additional VAC pumps should be purchased or rented until clear evidence of efficacy becomes available". The present report is an update of the 2005 report.

Wounds may result from many causes. Of those under consideration there are traumatic and surgical wounds that have not healed by first intention, wounds that complicate an underlying disease, such as diabetes or vascular insufficiency, and wounds that result from sustained pressure. Such wounds impair quality of life[2] and cause extensive consumption of health care resources in Canada[3] and worldwide[4].

OBJECTIVE

To systematically review any new evidence on the subject of the health effects of NPWT, and to estimate the costs of this treatment based on the published literature and the experience of users of this technology at the MUHC.

METHODS

The literature search in our previous 2005 report [1] was carried out up to March 27th 2005. We limited our current literature search to randomized controlled trials (RCTs) whose full texts were published in peer reviewed journals in English or French between January 1, 2005 and May 13th, 2010, using the online databases, PubMed and Embase, and the following key words : “vacuum” or “vacuum-assisted” or “VAC” or “negative pressure” or “suction dressing” or “subatmospheric” or “sub-atmospheric” or “subatmospheric pressure” or “NPWT”, and “Wound” or “injury” or “injuries” or “heal” or “healed” or “healing”, to identify RCTs published in 2005 or later. We also used the Health Technology Assessment (HTA) Database of the University of York (York, UK) to identify HTA reports and systematic reviews subsequent to 2005, and the references of systematic reviews and HTA reports to identify RCTs.

We included only studies that reported outcomes that described the rate of wound healing, such as: the mean/median days to complete healing, the percent of healing after a fixed period time, or the percent reduction in wound volume/depth/area after some given period of time. We did not consider the risk of infection a relevant outcome for measuring wound

healing, and the results of bacteriological studies were not extracted. Studies in which NPWT was used for skin grafts were not included. We also extracted the main outcomes reflecting the safety and costs of NPWT compared to other treatments. All articles were reviewed by both authors. Disagreements were resolved in the course of discussion with an internal reviewer. Because different authors use different outcome indicators it was impossible to carry out a meta-analysis.

Previous reviewers have rejected much of the evidence provided by RCTs. This appears to be partly because the quality of the RCTs was evaluated with standard instruments that were not entirely appropriate for the evaluation of trials of surgical outcomes. We therefore developed an instrument that we believe was more appropriate for the evaluation of these studies (see Appendix 1), and used it to classify the credibility of each study as; A (high), B (moderate) and C (low).

Cost analyses were conducted from the point of view of the MUHC. At this institution all appropriate wounds now receive NPWT. Accordingly we compared the cost of this treatment to the cost of the wound treatments that would be employed if NPWT was not available.

LITERATURE REVIEW: EFFECTIVENESS

HTAs/Systematic Reviews. We identified seven systematic reviews[5-11] published since 2005, of which six were recent (2008-09) [6-11]. Their principal conclusions are summarized in Table 1. Five[5, 7-11], concluded that the available evidence was insufficient to support the use of NPWT in wound therapy. One concluded that while all the studies reviewed indicated that NPWT therapy is more effective than conventional dressings for treatment of diabetic foot ulcers, " the quality of the studies were weak and the nature of the inquiries in terms of outcome and patient selection divergent"[7]. One concluded that NPWT was more effective than conventional treatments for lower limb wounds[6] .

We also identified six full HTA reports published since 2005[1, 2, 12-15], (See Table 1). A report by HAYES Inc. was not tracked[15]. A 2009 HTA[12] focused on the comparison of different NPWT technologies , but made no comparisons between any one technology and a control

therapy. The other four reports consistently concluded that the available evidence did not demonstrate the clinical effectiveness of NPWT therapy compared to conventional therapy[1, 2, 13, 14].

Randomized controlled trials. We identified 19 RCTs[4, 16-33] that compared NPWT with other therapies, of which one was a crossover trial[20]. Two studies[32, 33] that did not report any outcome to indicate the rate of wound healing were not included in formal evaluation. The 17[4, 16-31] remaining studies focused mostly on chronic wounds. In spite of considerable overlap concerning the type of wound studied, we arbitrarily divided studies into the following groups: diabetic foot ,7 ; mixed chronic and acute wounds, 5[23-27] ; and pressure ulcers, 3[4, 28, 29] ; and two studies of special applications of NPWT [30, 31]. Seven of these studies [16, 22, 26, 27, 30, 31, 33] had not been included in any previous reviews or HTA reports. The comparators in the selected RCTs include standard wound dressing, advanced moist wound therapy, and standard moist gauze dressing.

Clinical outcomes: The main clinical outcomes of the 17 RCTs can be found in Table 2, and the evaluation technique and additional study details in Table 3.

Diabetic foot: We identified seven RCTs[16-22] involving 580 patients with diabetic foot ulcers. Of these, two (quality A) [16, 17] , three (quality B) [18, 21, 22], and one (quality C) study[20] found evidence of significantly faster healing with NPWT.

Sepulveda et al., 2009 [16] (quality A), studied healing following diabetic toe amputation. The number of days necessary to achieve 90% granulation, as judged by a blinded evaluation of weekly photographs, in 12 treated vs. 12 controls, was clinically and statistically significantly (19 days vs. 32 days, p=0.007).

Blume et al., 2008[17] (quality A), studied the healing of diabetic foot ulcers. They based comparison on weekly evaluation of wound area, ulcer closure, and/or granulation tissue, in 169 treated vs. 166 control subjects. It is uncertain whether assessment was blinded. By 112 days 43% of the wounds were healed in the NPWT treated group versus 29% in the control group. (p=0.007).

Akbari et al., 2007[22] (quality B), studied the healing of diabetic foot ulcers. At the end of the three weeks observation period the NPWT group showed importantly greater reduction in the wound area (-12 mm^2) than the control group (-4 mm^2) (p=0.024).

Armstrong et al., 2005[18] (quality B), compared healing following diabetic foot amputation in 77 patients receiving NPWT and 85 controls, using planimetry of photographs evaluated by a blinded evaluator. By 112 days there was complete healing of 56% of the NPWT group versus 39% of the controls (p= 0.04). In a secondary analysis in 2007[34], the authors categorized wounds as acute (less than 30 days after amputation) or chronic (more than 30 days after amputation). Results in patients with NPWT were superior to moist wound therapy in both acute and chronic groups, consistent with results in 2005.

Etoz et al. ,2004 [21] (quality B), compared the rate of granulation in the wounds of 65 patients receiving NPWT with 65 controls, using paper cutouts to fit the wound area every 48 hours. The average reduction in surface area in the NPWT group, (evaluator unblinded) was clinically significant, 20.4 cm^2, versus 9.5 cm^2 in the controls (p=0.032).

McCallon et al., 2000[19] (quality C), in a study involving only five patients in each group, used computer biometrics to calculate surface area change based on surface area tracings made every 48 hours. They found fewer days to complete healing during the period of observation with NPWT than with control therapy (mean, SD: 23(17) vs. 43(33)) and a surface area change of -28.4% compared to + 9.5% in NPWT and control groups respectively. Though clinically significant, no statistical analysis was carried out due to the inadequate sample size.

Eginton et al., 2003[20] (quality C), evaluated seven wounds using a crossover design, with NPWT and control treatment applied for two weeks each. Changes in depth and volume, estimated by a blinded evaluator, were -49% and -7.7% (p=0.05), and -59% and - 0.1% respectively (p = <0.005).

Thus, each of these studies found clinically important acceleration of indices of healing in wounds treated with NPWT. Most were also statistically significant.

Mixed wounds, chronic and acute: We identified five RCTs involving 267 patients with chronic or a mix of chronic and acute wounds[23-27].

Perez et al., 2010[27] (Quality C), compared a simple home-made NPWT system with wet dressings for 40 patients with single acute and chronic wounds, including fasciitis, postoperative infection, venous leg ulcer, diabetic foot ulcer, etc. The time to achieve healing was faster in the NPWT group compared to the wet dressing group (16 days vs. 25 days, p=0.013).

Mody et al., 2008[26] (quality C), included 48 patients with various wounds, diabetic foot(15), pressure ulcers(11), cellulitis/fasciitis(11) and others. Seven out of 15 (47.6%) in the NPWT group and 16 out of 33 (48.4%) in the wet-to-dry gauze dressings group achieved satisfactory healing. For patients achieving satisfactory healing, the mean days to healing were 35.9 days and 28.4 days in NPWT and control groups, respectively (p=0.66).

Moues et al., 2007[25] (quality B), compared 29 patients treated with NPWT and 25 controls. They included patients with full-thickness wounds that could not be closed immediately "because of severely crushed tissue, infection or chronic character" [25]. Efficacy was judged by change in a semi-quantitative wound score based on “rubor, calor, and exudate”. The time until ulcers were considered to be ready for surgery was not clinically or statistically different (mean days, standard error (SE), 6(0.5) for NPWT vs. 7(0.8) for control, p=0.19). When wound scores were used to measure wound conditions relative to baseline, NPWT appeared to be more effective in improving wound conditions, reaching statistical significance in relative wound score on days 3, 6 and 8. In a subset of 15 NPWT vs 13 controls change in wound surface area was measured by a computer-generated program of tracings of surface area on polyethylene. Wound surface area diminished significantly more rapidly in the 15 treated patients than in the 13 control patients (3.8(0.5)% vs. 1.7(0.6)% per day, p<0.05). This outcome should be treated with reserve, since there is no indication of how the subset was selected.

Vuerstaek et al., 2006 [24] (quality B), included patients with chronic venous congestion or microangiopathic leg ulcer[24]. Wound progress was judged daily by one "independent research MD". The median time of healing in the NPWT group was less than the control group (29 vs. 45 days, $p<0.05$); and the median time of wound bed preparation in the NPWT group was less than the control group (7 vs. 17 days, $p<0.05$).

Braakenburg et al., 2006 [23] (quality C), included post-operative, diabetic and pressure wounds, of which 37% were acute and 63% chronic . Progress was judged by one MD based on examination of the wounds and photographs. The median healing time in the NPWT group was four days less than in the conventional group(16 vs. 20 days), $p=0.32$.

Thus, four of the five studies found improved healing compared to control treatment with NPWT therapy. In two (quality B[24], C[27]) this reached statistical significance, and in two (quality B[25], C[23]) it did not. In one study(quality C[26]) no difference was found in wound healing between NPWT and other therapies.

Pressure ulcer: We identified three RCTs[4, 28, 29] involving 68 patients (93 wounds) with pressure ulcer.

Wanner et al. [29] ,2003 (quality C), compared NPWT with conventional wet-to-dry/wet-to-wet techniques in the treatment of chronic pressure ulcers in paraplegic and tetraplegic patients. Outcome was evaluated by one individual who measured wound volume by saline injection each week. The two methods were equivalent in forming granulation tissue. The mean (SD) number of days to reach 50% of initial wound volume were 27(10) and 28(7) days in NPWT and conventional treatment groups, respectively.

Ford et al.[28] 2002 (quality C) compared NPWT in 25 wounds with treatment using three FDA-approved gel products developed by Healthpoint System (HP) in 15 wounds. Wounds were due to pressure ulcers, 43% accompanied by osteomyelitis. Wound dimensions were measured by plaster impressions evaluated by a blinded evaluator. By six weeks the average

percentage reductions with NPWT and HP, in volume/length/width/depth of wounds was NPWT: 52/37/40/34 vs. HP: 42/19/19/31, (p=0.46/0.1/0.11/0.9).

Joseph et al.[4] 2000 (quality B), compared NPWT in 18 chronic pressure wounds with traditional wet-to-moist dressings (18 wounds), using photographs and impression moulds. At six weeks follow up, the NPWT group showed greater percentage reduction of wound volume/depth than the control group (78/66 vs. 32/20, p=0.038/<0.001).

In summary, one study[4] (quality B) found clinically relevant and statistically significant evidence of better healing of pressure ulcers with NPWT, while two (quality C) [28, 29] found no evidence of benefit from use of NPWT in pressure ulcers in quadriplegic and tetraplegic patients, or in pressure ulcers complicated by osteomyelitis. Thus, at present the benefit of NPWT for pressure ulcers is inconclusive.

Special applications of NPWT : We identified two RCTs[30, 31] involving special applications of NPWT that seemed to be significantly different from other studies.

Bee et al. 2008 [31] (quality C), compared the use of NPWT with a newly developed Polyglactin Mesh to achieve temporary closure of the abdominal wall in 51 patients with extensive acute and subacute abdominal wall injuries. The delayed fascial closure rate in the NPWT group was slightly faster than in the control group (31% vs. 26%, not statistically significant), while the fistula rate in the NPWT group was higher (21% vs. 5%).

Huang et al. 2006 [30] (quality C), studied NPWT in 24 patients with acute necrotizing fasciitis.(12 NPWT vs 12 saline gauze dressings). The mean percentage reduction of wound dimension was unimportantly greater following NPWT (-47 % vs -41 %), (p>0.05).

Although they did not measure wound healing two other studies are of interest. Stannard et al. (2006) [32] evaluated 44 patients with post traumatic hematoma treated by NPWT or pressure dressing. The mean days of drainage were significantly less in the NPWT group, compared with pressure dressing (1.6 vs. 3.1 days, p=0.03), and infection rates were lower (8% vs 16%) with NPWT and pressure dressing groups respectively. In another study of 58

patients with 62 severe high-energy open fractures treated by NPWT or standard dressings Stannard et al. (2009) [33] found fewer deep infections in patients treated with NPWT, 2 (5.4%) with NPWT and 7 (28%) with standard dressings (p=0.024).

Safety issues.

Fourteen [4, 16-19, 21-28, 31] out of 17 RCTs reported adverse events (pain, bleeding, infection and osteomyelitis) following wound therapy (See Table 4).

Of three studies that reported the frequency of amputation following wound treatment, in two, Blume et al.[17] and Armstrong et al.[18], the risk of amputation was lower in NPWT groups, and in the third, Ford et al.[28], there was only one observed case of amputation which occurred in the NPWT group. However, it is difficult to ascertain whether amputation events are associated with treatment strategies. In Blume et al. [17] and Armstrong et al.[18], there were no significant differences of other complications between the two groups. In Ford et al.[28], authors did not find any other complications. In Etoz et al.[21], only one case of bleeding during dressing changes was observed. Sepulveda et al.[16], McCallon et al.[19] and Braakenburg et al.[23] observed a few cases with pain, bleeding and infections, but there did not seem to be significant differences between the two approaches. In Mody et al [26], both groups had two minor wound revisions (bedside débridement), and two leg pain or cramps at night were observed in the NPWT group. In Moues et al.[25], six major complications were observed in the NPWT group, including sepsis, necrosis, abscess(n=2), fistula and total skin graft failure; and three major complications were observed in the conventional group, including abscess, fistula and total skin graft failure. In Vuerstaek et al.[24] , 12 complications (including seven cutaneous damage) and seven complications were found in NPWT and conventional groups, respectively. In Joseph et al.[4], there were three complications in NPWT group, including two calcaneal fractures and one osteomyelitis; and there were 10 complications in the control group, including six wound infections, two fistulas and two osteomyelitis. No adverse events were reported in either group during the study in Akbari et al.[22]. In Perez et al [27], eight NPWT dressings had to be removed, due to hemorrhage (four cases), massive purulent secretion (three cases) and lost negative pressure (one case).In Bee et al [31], two cases were reported as failed by VAC.

In summary, there does not appear to be any clear evidence that NPWT is associated with an increase in complications.

Costs.

Six RCTs[23, 24, 26, 27, 30, 31] briefly reported on the costs of NPWT, while two studies, Moues et al. and Armstrong et al. presented full economic analysis in separate papers[18, 25, 35, 36]. Results of economic analyses varied greatly, since studies were conducted in different countries for very different types of wounds.

Perez et al. [27] in Haiti, compared conventional saline gauze treatment to treatment with a locally constructed NPWT apparatus. The total treatment cost per patient with acute or chronic wounds was 360 US$ and 271 US$ with NPWT and wet dressings, respectively (p=0.008)[27].

In the study of Mody et al., in India[26], the material costs of one dressing change with NPWT and conventional treatment (wet-to-dry gauze) were 2.27 US$ and 0.40 US$, respectively. The total material costs necessary for satisfactory closure of two pressure ulcers were 11.25 US$ and 22 US$ for treatment and control groups respectively.

Huang et al. in Taiwan[30], found the mean lengths of hospital stay were similar in both groups, 32 days by VAC and 34 days by control; the mean wound dressing material cost about 100 US$ per day for VAC versus 15 US$ per day for wet-to-dry dressing group; but daily nursing time was 4.8 minutes per day for VAC versus 19 minutes per day for wet-to-dry dressing.

Moues et al., in the Netherlands[25, 35], NPWT, comparing VAC to wet-to-dry gauze found significantly higher mean material costs (€414 vs. €15), significantly lower mean nursing costs (€33 vs. €83) and significantly lower mean hospitalization cost (€1,788 vs. €2,467). There was no significant difference in total costs per patient (€2,235 for NPWT vs. €2,565 for conventional therapy).

In the study of Armstrong et al. in the USA[18, 36], the average direct cost per patient (8 weeks or longer) was 27,270 US$ and 36,096 US$ in the NPWT and control group, respectively; for

patients to achieve healing, the average total cost was 25,954 US $ per patient treated with NPWT (n=43) compared with 38,806 US$ for “moist wound therapy” .

In Bee et al., in US[31], the material costs were 1,332 US$, 404 US$ and 474 US$ for VAC by KCI, polyglactin Mesh and so called traditional VAC dressing, respectively. Costs of operating room and hospitalization were not included in their analyses.

In Braakenburg et al. in the Netherlands[23], the total cost per patient for treatment of both acute and chronic wounds by NPWT and “modern wound” treatment were, €353 (range €111-1,503 and €273 (€40-1,123) respectively (p=0.09).

In Vuerstaek et al. in the Netherlands [24], the average total cost of NPWT for chronic leg ulcers was significantly less than conventional treatment ($3,881 vs $5,452. p=0.001), mainly due to the shorter duration of hospitalization with NPWT.

Thus, in summary, NPWT does not appear to be substantially more expensive than the treatments used as controls . In three studies[24, 35, 36] the overall costs of wound treatments, including hospitalization, nursing etc., were actually lower with NPWT than with control therapies , while in two[23, 27] costs were lower with control therapies.

NPWT THERAPY AT THE MUHC

Although there are two NPWT devices approved by Health Canada, only VAC by Kinetic Concepts, Inc. (KCI) has been used at MUHC. Both chronic and acute wounds are treated by VAC at MUHC but it is not used currently for skin grafts. Around half of the wounds treated are chronic and the others are acute/sub acute. Most VAC therapies are carried out at the Montreal General Hospital and the Royal Victoria Hospital, although a few cases are treated at the Lachine Hospital, the Montreal Children’s Hospital and the Chest Institute. The MUHC has recently updated all of its 23 VAC units.

Mr D'Souza is convinced that NPWT is equal or superior to all alternatives and at the present time at the MUHC all appropriate wounds are treated by NPWT. During the past year (March 2009 to February 2010), 229 patients received this treatment, involving 5,803 days of hospitalization. The average duration of treatment was 25 days (SD: 41 days. Range 1-334 days). For 57% of patients, therapy lasted 14 days or less. In general, hospitalization is not prolonged and may be shortened by the use of NPWT. However, there are numerous instances in which its use results in reduced hospital costs, such as when NPWT is used instead of repeated laparotomy in cases of abdominal injury and sepsis. (D'Souza)

Cost Estimates. Based on the actual cost per day of the VAC instruments used in fiscal year 2009-10 (see Table 6), the average cost of VAC at the MUHC is $36.30 per treatment day or $254.13 per week. Together with supplies and nursing costs, ***the estimated average cost of VAC is $486 per patient week*** (see Tables 5, 6).

As stated above, at the MUHC at this time almost all major wounds (other than clean post-operative incisions) receive VAC treatment. In order to estimate the cost of a comparator Mr D'Souza, the Senior Adviser for Wound and Stoma Programs made an estimate of the approximate type and quantity of dressing , and the frequency of dressing change that would be used for seven different types of wound, if NPWT treatment were not available. He also estimated the relative frequency of each wound type. In this way the average weighted cost of the treatment that would be used if NPWT were not available, including the costs of dressings, and nursing care, was estimated to be *(see Table 7):*
$42.71 per day or $299 per week. If we assume that this is estimate might vary by at most +/- 20%, the **estimated cost of NPWT (and limits of probability) would be $43 ($34- $51) per day or $299 ($238 - $357) per week**

Thus, NPWT treatment in hospital, costs approximately $187($129 - $248) per treatment week more than the alternate option. From the point of view of the health care system use of NPWT would cost less, and might even result in a net savings due to a reduction of overall treatment time. However, since its use probably does not shorten hospital stay, any more rapid healing associated with NPWT use will not influence costs experienced by the MUHC.

Budget impact. Average cost of NPWT in the MUHC (based on actual costs and actual treatment days over one year) **= $486 per week**.
The estimated cost of alternative treatment = **$299 ($238 - $357) per week.**
Thus, the budget impact of the decision to use NPWT instead of the alternate option for an assumed 829 patient weeks of treatment would be: **$155,023 ($106,941 - $205,592) per year**.

DISCUSSION

Effectiveness. Eight studies rated A or B[4, 16-18, 21, 22, 24, 25] found clinically important and statistically significant evidence of accelerated wound healing with NPWT. However, before concluding that this constitutes sufficient evidence on which to base policy there are several areas of concern that must be addressed.

The first is the possibility of publication bias. Peinemann et al [37] have drawn attention to the fact that "lack of access to unpublished study results data raises doubts about the completeness of the evidence-based on NPWT" . They reported that of 28 RCTs on the subject of NPWT identified at the end of 2007, six had been discontinued, and the status of three was unclear.

Of less concern is the question of conflict of interest. Although seven [4, 17, 18, 23-25, 28] of the 17 studies reported partial funding by the manufacturer, Kinetics Concepts Inc (KCI), and three[4, 18, 23] reported that authors received support from the same source to speak at meetings following the publication of the report, there is no evidence to suggest that that company employees were authors, handled data, or influenced the design or reporting of these studies

It is pertinent to ask in what way the evidence has changed since the time when most reviewers have concluded that the evidence is inadequate to support the conclusion that NPWT is an effective therapy. Undoubtedly the most important factor is the new evidence

contained in ten RCTs [16, 17, 22-27, 30, 31] published since 2006, eight [16, 17, 22, 23, 26, 27, 30, 31] of which were not included in even the most recent systematic Cochrane review [8]. Of these studies[16, 17] two (quality A), and six [22, 24, 25, 27, 30, 31] (quality B or C) reported clinical benefit of NPWT compared to control therapies.

In addition to this new evidence, we have considered some older evidence, discounted or discredited by previous reviewers, to be worthy of inclusion. For example, the Cochrane review[8] concluded that all the trials under consideration were of very poor quality, largely for the reason that these trials " have largely expressed the effects of TNP by indirect parameters such as rate of change in wound area or volume and not more patient relevant outcomes".
In the present report we have taken the opposite view. Although it might have been desirable to report only on the time to complete healing of wounds, the time to achieve partial healing as evidenced by reduction in wound surface area, depth, or volume is in our opinion highly patient relevant. Indeed, to discard such metrics it would be necessary to first explain why a reduction in wound size in a defined period of time would not relate to the time to complete healing.

Likewise in the HTA report published by the German Institute for Quality and Efficiency in Health Care (IQWiG) [2], the authors used four different categories to distinguish the “biometric quality” of publications; “*no evident deficiencies, minor deficiencies, major deficiencies* and *unclear*.” After thorough review, they considered each of seven RCTs to have *major deficiencies*. However, although each of these studies had defects, these did not all seem to us to be so egregious as to render the results unusable. For example, the IQWiG [2]reviewers were concerned that in the study of Wanner et al [29], "dressings in the NPWT group were only changed every two to seven days; this is less frequently than usual," and, "two of the 24 patients with pressure ulcers in the pelvic region were not considered in the evaluation. One of these patients was lost to follow-up, in the other patient the dressing for NPWT could not be fixed because of severe diarrhea. The ITT principle was thus violated." We do not believe either criticism should completely invalidate results. There is no obvious reason why reduced frequency of dressing change should improve the outcomes with NPWT. Likewise, it was

clearly an initial design error to attempt to use NPWT in the inguinal region. Though clearly a violation of the ITT principle there is no way such a withdrawal could lead to a biased result.

The 2006 Ontario HTA report[13] also concluded that five of the six RCTs under consideration were of low or very low quality. These reviewers used the GRADE system of classification[38] a system that depends on subjective evaluation of study qualities such as inconsistency of results, indirectness of evidence, imprecision, and reporting bias. It does not result in a quantifiable, repeatable scoring system.

A particular problem of scoring the quality of NPWT studies lies in the difficulty of blinding the evaluation of the outcomes. Indeed, it seems that even independent evaluators cannot be blinded because use of NPWT creates a wound appearance that is easily identifiable [18, 23] . Since it is counter-productive to penalise studies for failing to reach non-achievable criteria, we sought a numerical scoring system that would be applicable to wound healing studies. After considering standard instruments such as Cochrane[39], Jadad[40], Physiotherapy Evidence Database (PEDro) scale[41], and the Dutch Cochrane Collaboration Checklist [8] we decided to develop a specific instrument, to evaluate the quality of RCTs of this type of wound therapy. In this instrument a score is deducted for absence of specific quality determinants. The score must recognize that an index of wound healing that depends on unblinded, but relatively objective measurement of wound depth, area, or volume is less susceptible to bias than an unblinded subjective evaluation of "wound healing". Using this instrument, which is described in detail in Appendix 1 , a convincing number of studies are considered to have produced acceptable evidence (rated A or B).

Lastly, although not easily quantifiable, patient preference is important. According to D'Souza many patients report that with NPWT they feel more comfortable and in consequence use less pain medication, return to ambulation more rapidly, and feel more independent. They have a feeling of increased security and safety because they feel supported (braced) by the VAC. In addition they are able to socialize and sometimes even return to work, and as a result feel better about their overall situation. Spouses reportedly say that they are now able

to sleep in the same bed again because they feel comfortable that their partner is not going to be hurt by something they do during sleep.

CONCLUSIONS

- **Although additional RCTs of substantial size are still necessary to establish the value of NPWT for certain types of wound, there is now sufficient evidence to conclude that the healing of diabetes-associated chronic lower extremity wounds can be accelerated by its use.**
- **There is less convincing evidence that the healing of several other types of wound can also be accelerated by use of NPWT.**
- **The evidence of the use of NPWT for the treatment of pressure ulcers, necrotising fasciitis, and wounds complicated by osteomyelitis remains conflicting.**
- **The increased cost of using NPWT at the MUHC, compared to the alternate available option is approximately $187 per patient week, and the current budget impact approximately $150,000 per year.**

RECOMMENDATIONS

- **In view of the evidence that NPWT promotes the healing of many types of wound, and because at this time NPWT is the accepted standard treatment used throughout the MUHC it is recommended that the MUHC should continued to fund this technology .**

- **The *Programme for Wound Care* should be encouraged to undertake an RCT to evaluate the effectiveness of NPWT and its influence on length of hospital stay and costs for the treatment of pressure ulcers, necrotising fasciitis, and wounds complicated by osteomyelitis.**

TABLES

Table 1: Systematic reviews / HTA reports published since 2005 Principal conclusions

Author (year)	Title	Conclusions
Review		
Ubbink et al. [8] (2009)	Topical negative pressure for treating chronic wounds	There is a lack of good quality RCTs evaluating TNP as a treatment for chronic wounds and robust information on the effects of TNP on healing, quality of life, pain and costs is lacking. (In main text)
Sadat et al. [6] (2008)	Efficacy of TNP (topical negative pressure) on lower limb wounds: a meta-analysis	Compared with conventional treatment, topical negative pressure significantly reduced healing times and increased the number of healed wounds in patients with lower limb ulcers
Gregor et al. [10] (2008)	Negative Pressure Wound Therapy A Vacuum of Evidence?	Although there is some indication that NPWT may improve wound healing, the body of evidence available is insufficient to clearly prove an additional clinical benefit of NPWT.
Ubbink et al. [9] (2008)	A systematic review of topical negative pressure therapy for acute and chronic wounds	There is little evidence to support the use of TNP in the treatment of wounds.
Noble-Bell et al. [7] (2008)	A systematic review of the effectiveness of negative pressure wound therapy in the management of diabetes foot ulcers	The NPWT therapy is more effective than conventional dressings. The quality of the studies were weak and the nature of the inquiries in terms of outcome and patient selection divergent.
Boogaard et al. [11] (2008)	The effectiveness of topical negative pressure in the treatment of pressure ulcers: a literature review	TNP has not been proven to be more effective than various control interventions.
Mendonca et al.[5] (2006)	Negative-pressure wound therapy: a snapshot of the evidence	The clinical effectiveness of NPWT is still unclear. The few RCTs have very mixed results. Evidence for the use of TNP to enhance wound healing in patients with decubitus ulcers, diabetes and peripheral vascular disease and to improve skin graft take is lacking.
HTA		
Ontario[13] (2006)	Negative pressure wound therapy: an evidence-based analysis	Based on the evidence to date, the clinical effectiveness of NPWT to heal wounds is unclear.
Germany[2] (2006)	Negative pressure wound therapy	There are at present no results of adequate reliability which provide proof of the superiority of NPWT in comparison with conventional therapy.
Gastelu-Iturri[14] (2005)	Vacuum-Assisted Closure Effectiveness for Chronic Wounds Therapy (Technical report)	Existing clinical trials show poor methodological quality and a sample size too small for detection of statistically significant differences between NPWT and conventional treatments.
Costa [1] (2005)	Vacuum-assisted wound closure therapy (V.A.C)	There was insufficient evidence to justify recommending routine use of VAC therapy.

Note: One review of treatment of pressure ulcers[42] and the other one of healing of chronic ulcers of the foot in diabetes[43] also included studies by VAC therapy in their specific scenarios, but the conclusion of those two studies were not presented since the aim of their studies were different from ours.

TABLE 2:. Principal Outcomes

Author (year)	Pathology	N NPWT/C	Outcomes Evaluated	Outcome NPWT	Outcome Control	P value	Quality Rating
Sepulveda et al.[16] (2009)	Diabetic toe amputation	12/12(p)	1) Days to 90% granulation, M (SD) #. 2) N(%) granulation around 90%	18.8(6) 12(100)	32.3(13.7) 11(92)	**0.007** NA	**A**
Blume et al.[17] (2008) *	Diabetic foot ulcer	169/166(p)	1) N(%) healing by 112 days 2) Median days of complete ulcer closure	73(43) 96	48(29) Cannot be estimated	**0.007** **0.001**	**A**
Akbari et al.[22] (2007)	Diabetic foot ulcer	9/9	1) Change in wound area, M (SD) mm^2 2) N(%) of foot ulcer improvement	-11.8(9.5) 5(56)	-3.7(3.1) 1(11)	**0.03** **<0.05**	**B**
Armstrong et al.[18] (2005)*	Following diabetic foot amputation	77/85(p)	1) N(%) complete healing by 112 days 2) Median days to >76% granulation (IQR)	43(56) 42(40-56)	33(39) 84(57-112)	**0.040** **0.002**	**B**
Etöz et al. [21] (2004)	Diabetic foot ulcer	12/12(p)	1) Days to almost granulation, M (SD) 2) Changes of wound surface area (cm^2)	11.3(5.5) 20.4	15.8(2.5) 9.5	**0.05** **0.032**	**B**
Eginton et al. [20] (2003) *	Diabetic foot wound	Crossover 7(w)	1) % change in depth of wound M(SD)#. 2) % change in volume of wound M(SD)#.	-49(11) -59(10)	-7.7(5) -0.1(15)	**<0.05** **<0.005**	**C**
McCallon et al.[19] (2000)	Diabetic foot ulcer	5/5(p)	1) Days to healing. Mean (SD) # 2) % change in wound surface area, M(SD) #	23(17) **-** 28(24)	43(33) **+**10(17)	0.31Δ 0.24Δ	**C**
Perez et al.[27] (2010)	Single chronic or acute wound	20/20	1) Days to wound closure, M 2) N(%) healing by 30 days after closure	16.3 18(90)	25.4 19(95)	**0.013** 0.302	**C**
Mody et al.[26] (2008)	Aute/Chronic Mixed: Diabetic, Pressure, Fasciitis	15/33	1) N(%) satisfactory healing	7(47)	16(48)	N.A.	**C**
Moues et al.[25] (2007) *	Chronic & infected.	29/25(p)	1) Relative wound score at day 10. 2) Days to readiness for surgery M (SE)	26 6(0.52)	57 7(0.81)	>0.05† 0.19	**B**
Vuerstaek et al.[24](2006) *	Chronic venous or microsngiopathic leg ulcer	30/30(p)&	1) Days to healing. Median (95%CI) 2) N(%) healed in 43 days. 3) Wound preparation days. Mean(95%CI)	29(26-33) 25(90) 7(5.7-8.3)	45(36-54) 12(48) 17(10-24)	**<0.05** **<0.001‡** **0.005**	**B**
Braakenburg et al.[23](2006)*	Wounds.37%acute ; 63%Chronic	32/33(p)	Days to healing, Median (95%CI).	16(9-23)	20(16-24)	0.32	**C**

Author (year)	Pathology	N NPWT/C	Outcomes Evaluated	Outcome NPWT	Outcome Control	P value	Quality Rating
Wanner et al.[29] (2003)	Pressure Ulcers in para/tetraplegia	11/11(p)	Days to 50% reduction in wound volume. M (SD)	27(10)	28(7)	0.9	**C**
Ford et al.[28] (2002) *	Pressure Ulcer. 43% osteomyelitis.	20/15(w) (22p in total)	1) N(%) complete healing by 6 weeks 2) % change in wound volume 3) % change in wound Length/ Width/ Depth	2(10) -52 -37/-40/-34	2(15) -42 -19-/-19/-31	NA 0.46 0.1/ 0.11/0.9	**C**
Joseph et al.[4] (2000) *	Chronic wounds. 79% due pressure.	18/18(w) (24p)	1) % change in wound volume 2) % change in wound depth	-78 -66	-30 -20	**0.038** **<0.001**	**B**
Huang et al.[30] (2006)	Acute necrotizing fasciitis	12/12	1) % change in wound dimension 2) % change in drainage volume	-47 -49	-41 -39	>0.05 >0.05	**C**
Bee et al.[31] (2008)	Abdominal incision	31/20	1) N(%)delayed fascial closure 2) N(%) fistula	9/29(31) 6/29(21)	5/19(26) 1/19(5)	>0.05 0.14	**C**

Abbreviations: NPWT=negative pressure wound therapy; C=control; p= Patients; w= Wounds; NA=not applicable; N=number; M=mean; IQR= interquartile range; SD=standard deviation; SE=standard error; Md=median.
* Study supported or partly supported by manufacturer; or one or more authors received research grants, etc. from the manufacturer.
&: Although 9 of 60 patients had 2 or 3 ulcers, only 1 ulcer per patient was analyzed.
#: Authors did not mention the meaning of figures in brackets/± following the means. We presumed those are standard deviation (SD).
∆: Authors did not conduct statistical analysis for the small sample size. To obtain p value, we performed t-test by assuming t-distribution of samples. What we did was not robust.
†: At day 3, 6 and 8, results favored the NPWT treatment group significantly. Results on other days favored NPWT treatment also, but no statistical differences between two groups.
‡: Authors did not state the p value. We used chi square or exact chi square test to calculate the p value.
$: A sub-group in this study was patients with fractures. The duration of recruiting patients (June 2001 to March 2003) was overlapped by same authors' study published in 2009, whose enrollment duration was from June 2001 to August 2006. Also, the publication in 2009 has the larger sample size (58 vs. 44). As we did not receive any responses to our request regarding the independence issues of two studies, we excluded the sub-group of fractures in 2006 in our analyses.

TABLE 3: Evaluation Technique, and Additional quality related data

Author (year)	Age: NPWT/C	Treatment in control group	Observation period	Evaluation Technique
Sepulveda et al.[16] (2009)	62/62	Standard wound dressing	Until 90 % granulation	Independent, blinded evaluation of weekly photos
Blume et al.[17] (2008)	58/59	Advanced Moist Wound Therapy	112 days	Weekly and bi-weekly examination with tracing of wound area, ulcer closure, and/or granulation tissue.
Akbari et al.[22] (2007)	58/58	Conventional therapy, saline wound dressing	3 weeks	Ulcer surface area was estimated by point grid overlays with point-counting techniques.
Armstrong et al.[18] (2005)	57/60	Moist wound therapy	112 days	Planimetry of photographs, Independent evaluation.
Etöz et al. [21] (2004)	66/65	Moist gauze dressings	Until granulation	Use a sterilized milimetric paper with a pen, and cut paper to fit the wound. Every 48 hours.
Eginton et al.[20] (2003)	N.A.	Moist gauze dressings	8 weeks	Weekly 3D photographs. Blinded evaluation.
McCallon et al.[19] (2000)	55/50	Saline-moistened gauze	Until healing	Photography. Acetate Tracing
Perez et al.[27] (2010)	49/44	Saline-soaked gauze dressings	Until healing. Complete at 30 d	Wound was copied on a sheet of paper. The area drawn was cut and weighed to calculate the area surface according to the paper density.
Mody et al.[26] (2008)	53/59	Wet-to-dry gauze dressings	VAC: 33 days Control: 26 days	Wound size was determined using computer-aided measurements of digital photographs. Depth was assessed using a centimeter ruler at the maximum dimension for depth.
Moues et al.[25] (2007)	48/48	Standard moist gauze therapy	30 days	Daily evaluation, visual score for rubor, calor, exudate, etc.
Vuerstaek et al.[24] (2006)	74/72	Standard wound dressing	43 days	Daily clinical evaluation by 1 independent research MD
Braakenburg et al.[23] (2006)	66/69	Modern wound dressing		Assessment by one MD. Photos. wound area measured
Wanner et	49/53	Wet-to-dry/wet-to-wet	To 50% loss	One individual. Weekly volume by saline injection

Author (year)	Age: NPWT/C	Treatment in control group	Observation period	Evaluation Technique
al.[29] (2003)			of volume	
Ford et al.[28] (2002)	42/54	Healthpoint System	6 weeks	Blinded measurement of wounds & plaster impressions
Joseph et al.[4] (2000)	56/49	Standard moist gauze dressings	3-6 weeks	Blinded clinical evaluation. Photos. Volume by impression molds
Huang et al.[30] (2006)	58/63	Saline gauze	VAC, 32 days Control, 34 days	N.A.
Bee et al.[31] (2008)	44/37	Polyglactin 910 mesh	Delayed primary closure	N.A.

Abbreviations: NPWT=negative pressure wound therapy; C=control; Rx= Latin word "recipe" meaning "to take."; N.A.=not available; NS= not state; ITT= intention to treat.

TABLE 4: Adverse events

Author (year)	Adverse events
Sepulveda et al.[16] (2009)	No re-amputation, asepsis or mortality in both groups. NPWT group: 1 bleeding; Conventional group: 1 pain and 1 infection.
Blume et al.[17] (2008)	N(%) of re-amputations, NPWT: 7 (4.1) vs. Control: 17(10.2), p=0.035. There were no significant differences of other complications between two groups. N(%) of Edema, NPWT: 5 (3) vs. Control: 7(4.2) ; wound infection, NPWT: 4 (2.4) vs. Control: 1 (0.6); cellulitis, NPWT: 4 (2.4) vs. Control: 1 (0.6); osteomyelitis, NPWT: 1 (0.6) vs. Control: 0 (0); *Staphylococcus* infection, NPWT: 1 (0.6) vs. Control: 0 (0); infected skin ulcer, NPWT: 1 (0.6) vs. Control: 2 (1.2).
Akbari et al.[22] (2007)	No adverse events were reported in either group during the study.
Armstrong et al.[18] (2005)	40 (52%) patients in NPWT group and 46 (54%) in control group had one or more adverse events (p=0.875). N(%) of re –amputations, NPWT: 2 (3) vs. Control: 9(11), p=0.06; infections and infestations in common organ system, NPWT: 25(32) vs. Control: 27(32); wound infections, NPWT: 13(17) vs. Control: 5(6); treatment-related adverse event, NPWT: 9(12) vs. Control:11(13).
Etöz et al. [21] (2004)	No infection in both groups. One bleeding in NPWT group during dressing changes.
Eginton et al.[20] (2003)	N.A.
McCallon et al.[19] (2000)	NPWT: pain in short duration; minor capillary disruption with NPWT foam dressing removal. Control: not report.
Perez et al.[27] (2010)	Eight NPWT dressings had to be removed after previous dressing change, due to hemorrhage (4 cases), massive purulent secretion (3 cases) and loss negative pressure (1 case).
Mody et al.[26] (2008)	NPWT: two minor wound revisions (bedside débridement) and two leg pain or cramps at night. Conventional: two minor wound revisions (bedside débridement).
Moues et al.[25] (2007)	Serious (sepsis and necrosis), and minor complications occurred in 2 and 4 NPWT treated patients respectively, and minor complications only in 5 control patients. Following post-operative closure in 46 patients, complications occurred in 9 of 21 control patients (43%), and 8 of 25 with NPWT(32%)
Vuerstaek et al.[24] (2006)	NPWT: 12 complications, including 7 cutaneous damage, 3 pain, 1 erysipelas and 1 non-healing ulcer. Conventional: 7 complications, including 2 cutaneous damage, 2 postoperative bleeding, 1 pain, 1 infection and 1 non-healing ulcer.
Braakenburg et al.[23] (2006)	Two patients had to discontinue treatment in the NPWT group due to pain during dressing changes. No other complications occurred. Also, authors found there were some technical problems with NPWT initially, probably due to the learning curve.
Wanner et al.[29] (2003)	N.A.

Author (year)	Adverse events
Ford et al.[28] (2002)	NPWT: 1 patient with sepsis, requiring amputation. Control: none.
Joseph et al.[4] (2000)	NPWT: 3 complications, 2 calcaneal fractures and 1 osteomyelitis. Control: 10 complications, 6 wound infections, 2 fistulas and 2 osteomyelitis.
Huang et al.[30] (2006)	N.A.
Bee et al.[31] (2008)	Two cases failed by VAC use and then underwent polyglactin mesh placement successfully.

Table 5: V.A.C.® treatment cost ($ Canadian)

Equipment	Unit cost	Cost per patient (1 week)
V.A.C.® ATS pump	$36.3/treatment day	$36.3 x 7 = $254.13*
Dressings (includes tubing†)	Garnufoam - small : $47.13 - med : $59.07 - large : $69.80 Versafoam - small : $51.68 - large : $67.02 Average = $58.94	$58.94 x 3 = $176.82
Other material	$3.5 per dressing change	$3.5 x 3 = $10.5
Canister	$44.64	$44.64
Nursing salaries	$41.02/hr	$41.02/hr x 30min x 3 = $61.53
Total cost (materials and nursing)		**Average = $486**

Hr: hour; na = not applicable. * See Table 6

Table 6: Actual cost per day VAC

	unit price	qty	Total
Purchase cost	$19,900	23	$457,700
VAC upgrade 09-10 (total)			$ 66,000
Expected life (yr)			5
Cost per year - equipment			$104,740
Decontamination contract	$ 2,125	23	$ 48,875
Extended Warranty	$ 1,250	23	$ 28,750
Total direct yearly cost			$182,365

2009-10 actuals	Apr.	May	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.	Total
# of days per month	30	31	30	31	31	30	31	30	31	31	28	31	
Maximum usage	75%	75%	75%	75%	75%	75%	75%	75%	75%	75%	75%	75%	
# of VAC pump	23	23	23	23	23	23	23	23	23	23	23	23	
Available treatment days	518	535	518	535	535	518	535	518	535	535	483	535	6,296
Actual # of days	471	528	531	670	618	618	484	415	371	454	386	257	5,803
# of extra treatment days	-	-	14	135	83	101	-	-	-	-	-	-	333
Cost per day (rental)	$ 85	$ 85	$ 85	$ 85	$ 85	$ 85	$ 85	$ 85	$ 85	$ 85	$ 85	$ 85	$ 85
Extra rental cost	$ -	$ -	$ 1,190	$11,475	$ 7,055	$8,585	$-	$ -	$ -	$ -	$ -	$ -	$28,305

Total rental cost 2009-10	$ 28,305
Total 2009-10 VAC cost	**$210,670**
# of treatment days	5,803
Actual cost per treatment day	**$ 36.30**
Cost for 7 treatment days	$ 254.13

Table 7: Cost of alternative treatment to NPWT (Dressing change: once per day)

Wound Type	Dressings /Treatment		Unit Cost $	Dressings $/day	Nursing $/day‡	Total $/day	Frequency % all wounds	Weighted cost $/day
Abdominal uninfected (15%)	Mesalt	3	0.99	2.97	13.67	34.43	4.0	1.38
	+ Mepilex (20x20)	1	15.89	15.89				
	Dressing tray	1	1.90	1.90				
Abdominal infected (85%)	Acticoat(Silver)	3	10.73	32.19	13.67	63.65	26.0	16.55
	+ Mepilex (20x20)	1	15.89	15.89				
	Dressing tray	1	1.90	1.90				
Diabetic foot †	Anticoat	3	10.73	32.19	13.67	58.49	6.25	3.66
	+ Mepilex (10x10)	1	10.73	10.73				
	Dressing tray	1	1.90	1.90				
Diabetic foot †	OR Iodosorb	1	8.70	8.70	13.67	35	6.25	2.19
	+ Mepilex (10x10)	1	10.73	10.73				
	Dressing tray	1	1.90	1.90				
Pressure ulcer	Mesalt	3	0.99	2.97	13.67	34.43	20	6.89
	+Mepilex (20x20)	1	15.89	15.89				
	Dressing tray	1	1.90	1.90				
Vascular Insufficiency	Melgisorb	2	3.47	6.94	13.67	33.24	12.5	4.16
	+ Mepilex (10x10)	1	10.73	10.73				
	Dressing tray	1	1.90	1.90				
Sternal wound	AMD	1	0.12	0.12	13.67	31.58	25.0	7.90
	+Mepilex(20x20)	1	15.89	15.89				
	Dressing tray	1	1.90	1.90				
Weighted cost	--		--	--	--	--	100	**42.71**

20x20: 20cm x 20 cm; 10x10: 10 cm x 10 cm.

‡: It was assumed that each dressing takes 20 minutes. Salary rate of nursing: $41.02 per hour.

†: There are two types of dressing for diabetic foot. We estimated that each dressing is used for half patients.

Table 8: Quality Scoring of RCTs (See Appendix)

STUDY (YEAR)	SELECTION BIAS Random Baseline Technique Equality		DETECTION BIAS Blinded Evaluation Subject Objective Outcome	Outcome	ATTRITION BIAS Withdrawals and Dropouts Excess Described ITT	SAMPLE SIZE	SCORE	QUALITY RATING
Sepulveda[16] (2009)	A1 0	A4 0	B1 0		C1 0 na 0	0	10	**A**
Blume(2008)	A1 0	A4 0		B4 -1	Kaplan-Meier Survival analysis	0	9	**A**
Akbari[22] (2007)	A1 0	A4 0		B4 -1	C2 -1 C8 -1	0	7	**B**
Armstrong[18] (2005)	A1 -1	A4 0		B3 -1	Kaplan-Meier Survival analysis	0	8	**B**
Etöz[21] (2004)	A3 -1	A4 0		B3 -1	C1 0 na 0	0	8	**B**
Eginton[20] (2003)	A1 0	A6 -1		B1 0	C3 -2 C5 -2	D 2 -1	4	**C**
McCallon[19] (2000)	A2 -2	A4 0		B3 -1	C1 0 na 0 C8‡ 0	D 2 -1	6	**C**
Perez[27] (2010)	A1 0	A4 0		B4 -1	C3 -2 C9 -2	0	5	**C**
Mody[26] (2008)	A1 0	A4 0		B3 -1	C3 -2 C5 -2	0	6	**C**
Moues[25] (2007)	A1 0	A4 0	B2 -2		C2 -1 C8† 0	0	7	**B**
Vuerstaek[24] (2006)	A1 0	A4 0	B2 -2		C2 - 1	0	7	**B**
Braakenburg[23] (2006)	A1 0	A4 0		B3 -1	C3 -2 C5 -2	0	5	**C**
Wanner[29] (2003)	A3 -1	A5 -2		B3 -1	C1 0 na 0 C8‡ 0	0	6	**C**
Ford[28](2002)	A3 -1	A6 -1		B1 0	C2 -1 C9 -2	0	5	**C**
Joseph[4] (2000)	A1 0	A5 -2	B1 0		Kaplan-Meier Survival analysis	0	8	**B**
Huang [30] (2006)	A2 -1	A4 0		B4 -1	C2 -1 C8 -1	0	6	**C**
Bee.[31] (2008)	A1 -0	A4 0		B4 -1	C2 -1 C9 -2	0	6	**C**

ITT=intension to treat; na= not applicable. †: Although authors did not mention using intention to treat, it appeared they used it in the analyses.
#: Authors did not mention using intention to treat, and it appeared they did not use it in the analyses, too.
‡: Although authors did not mention using intention to treat, due to no withdrawal/ dropouts, they do not lose points.

REFERENCES

(1) Costa V, Brophy J, McGregor M. *Vacuum-Assisted Wound Closure Therapy (V.A.C.®) [Technology Report No 19].* Montreal: Technology Assessment Unit of the McGill University Health Centre, Canada. *http://www mcgill ca/files/tau/VAC_REPORT_FINAL pdf* 2007. Accessed January 29, 2010.

(2) Institute for Quality and Efficiency in Health Care. Negative pressure wound therapy;[2006 No. 04], Cologne, Germany. *http://www iqwig de/download/N04-03_Final_report_Negative_pressure_wound_therapy pdf* ,2008.

(3) Hurd T, Zuiliani N, Posnett J. Evaluation of the impact of restructuring wound management practices in a community care provider in Niagara, Canada. *Int Wound J* 2008;5(2):296-304.

(4) Joseph E, Hamori CA, Bergman S, Roaf E, Swann NF, Anastasi GW. A prospective randomized trial of vacuum-assisted closure versus standard therapy of chronic nonhealing wounds. *Wounds-A Compendium of Clinical Research and Practice* 2000;12(3):60-67.

(5) Mendonca DA, Papini R, Price PE. Negative-pressure wound therapy: a snapshot of the evidence. *Int Wound J* 2006;3(4):261-271.

(6) Sadat U, Chang G, Noorani A, Walsh SR, Hayes PD, Varty K. Efficacy of TNP on lower limb wounds: a meta-analysis. *J Wound Care* 2008;17(1):45-48.

(7) Noble-Bell G, Forbes A. A systematic review of the effectiveness of negative pressure wound therapy in the management of diabetes foot ulcers. *Int Wound J* 2008;5(2):233-242.

(8) Ubbink DT, Westerbos SJ, Evans D, Land L, Vermeulen H. Topical negative pressure for treating chronic wounds. *Cochrane Database Syst Rev* 2009;(3):CD001898.

(9) Ubbink DT, Westerbos SJ, Nelson EA, Vermeulen H. A systematic review of topical negative pressure therapy for acute and chronic wounds. *Br J Surg* 2008;95(6):685-692.

(10) Gregor S, Maegele M, Sauerland S, Krahn JF, Peinemann F, Lange S. Negative pressure wound therapy: a vacuum of evidence? *Arch Surg* 2008;143(2):189-196.

(11) Boogaard MVD, Laat ED, Spauwen P, Schoonhoven L. The effectiveness of topical negative pressure in the treatment of pressure ulcers: a literature review. *Eur J Plast Surg* 2008;31(1):1-7.

(12) Sullivan N, Snyder DL, Tipton K, Uhl S, Schoelles KM. Negative Pressure Wound Therapy Devices [Technology Report ID: WNDT1108]. Rockville: Agency for

Healthcare Research and Quality, Department of Health and Human service, United States. *http://www ahrq gov/Clinic/ta/negpresswtd/negpresswtd pdf* 2009. AccessedJanuary 29, 2010.

(13) Medical Advisory Secretariat. Ontario Health Technology Assessment Series 6(14), Canada. *http://www health gov on ca/english/providers/program/mas/tech/reviews/pdf/rev_npwt_070106 pdf* 2006. AccessedJanuary 29, 2010.

(14) Gastelu-Iturri B.J., Atienza M.G. *Vacuum-Assisted Closure Effectiveness for Chronic Wounds Therapy (Technical report)*. Santiago de ComPostela: Galician Agency for Health Technology Assessment (AVALIA-T); 2005.

(15) HAYES Inc. *Negative pressure wound therapy for wound healing*. Lansdale: HAYES, Inc.; 2007.

(16) Sepulveda G, Espindola M, Maureira M et al. [Negative-pressure wound therapy versus standard wound dressing in the treatment of diabetic foot amputation. A randomized controlled trial]. *Cir Esp* 2009;86(3):171-177.

(17) Blume PA, Walters J, Payne W, Ayala J, Lantis J. Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers: a multicenter randomized controlled trial. *Diabetes Care* 2008;31(4):631-636.

(18) Armstrong DG, Lavery LA. Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomized controlled trial. *Lancet* 2005;366(9498):1704-1710.

(19) McCallon SK, Knight CA, Valiulus JP, Cunningham MW, McCulloch JM, Farinas LP. Vacuum-assisted closure versus saline-moistened gauze in the healing of postoperative diabetic foot wounds. *Ostomy Wound Manage* 2000;46(8):28-32, 34.

(20) Eginton MT, Brown KR, Seabrook GR, Towne JB, Cambria RA. A prospective randomized evaluation of negative-pressure wound dressings for diabetic foot wounds. *Ann Vasc Surg* 2003;17(6):645-649.

(21) Etoz A, Ozgenel Y, Ozcan M. The use of negative pressure wound therapy on diabetic foot ulcers: A preliminary controlled trial. *Wounds* 2004;16(8):264-269.

(22) Akbari A, Moodi H, Ghiasi F, Sagheb HM, Rashidi H. Effects of vacuum-compression therapy on healing of diabetic foot ulcers: randomized controlled trial. *J Rehabil Res Dev* 2007;44(5):631-636.

(23) Braakenburg A, Obdeijn MC, Feitz R, van Rooij IA, van Griethuysen AJ, Klinkenbijl JH. The clinical efficacy and cost effectiveness of the vacuum-assisted closure technique in the management of acute and chronic wounds: a randomized controlled trial. *Plast Reconstr Surg* 2006;118(2):390-397.

(24) Vuerstaek JD, Vainas T, Wuite J, Nelemans P, Neumann MH, Veraart JC. State-of-the-art treatment of chronic leg ulcers: A randomized controlled trial comparing vacuum-assisted closure (V.A.C.) with modern wound dressings. *J Vasc Surg* 2006;44(5):1029-1037.

(25) Moues CM, van den Bemd GJ, Heule F, Hovius SE. Comparing conventional gauze therapy to vacuum-assisted closure wound therapy: a prospective randomized trial. *J Plast Reconstr Aesthet Surg* 2007;60(6):672-681.

(26) Mody GN, Nirmal IA, Duraisamy S, Perakath B. A blinded, prospective, randomized controlled trial of topical negative pressure wound closure in India. *Ostomy Wound Manage* 2008;54(12):36-46.

(27) Perez D, Bramkamp M, Exe C, von RC, Ziegler A. Modern wound care for the poor: a randomized clinical trial comparing the vacuum system with conventional saline-soaked gauze dressings. *Am J Surg* 2010;199(1):14-20.

(28) Ford CN, Reinhard ER, Yeh D et al. Interim analysis of a prospective, randomized trial of vacuum-assisted closure versus the healthpoint system in the management of pressure ulcers. *Ann Plast Surg* 2002;49(1):55-61.

(29) Wanner MB, Schwarzl F, Strub B, Zaech GA, Pierer G. Vacuum-assisted wound closure for cheaper and more comfortable healing of pressure sores: a prospective study. *Scand J Plast Reconstr Surg Hand Surg* 2003;37(1):28-33.

(30) Huang WS, Hsieh SC, Hsieh CS, Schoung JY, Huang T. Use of vacuum-assisted wound closure to manage limb wounds in patients suffering from acute necrotizing fasciitis. *Asian J Surg* 2006;29(3):135-139.

(31) Bee TK, Croce MA, Magnotti LJ et al. Temporary abdominal closure techniques: a prospective randomized trial comparing polyglactin 910 mesh and vacuum-assisted closure. *J Trauma* 2008;65(2):337-342.

(32) Stannard JP, Robinson JT, Anderson ER, McGwin G, Jr., Volgas DA, Alonso JE. Negative pressure wound therapy to treat hematomas and surgical incisions following high-energy trauma. *J Trauma* 2006;60(6):1301-1306.

(33) Stannard JP, Volgas DA, Stewart R, McGwin G, Jr., Alonso JE. Negative pressure wound therapy after severe open fractures: a prospective randomized study. *J Orthop Trauma* 2009;23(8):552-557.

(34) Armstrong DG, Lavery LA, Boulton AJ. Negative pressure wound therapy via vacuum-assisted closure following partial foot amputation: what is the role of wound chronicity? *Int Wound J* 2007;4(1):79-86.

(35) Moues CM, van den Bemd GJ, Meerding WJ, Hovius SE. An economic evaluation of the use of TNP on full-thickness wounds. *J Wound Care* 2005;14(5):224-227.

(36) Apelqvist J, Armstrong DG, Lavery LA, Boulton AJ. Resource utilization and economic costs of care based on a randomized trial of vacuum-assisted closure therapy in the treatment of diabetic foot wounds. *Am J Surg* 2008;195(6):782-788.

(37) Peinemann F, McGauran N, Sauerland S, Lange S. Negative pressure wound therapy: potential publication bias caused by lack of access to unpublished study results data. *BMC Med Res Methodol* 2008;8:4.

(38) Atkins D, Best D, Briss PA et al. Grading quality of evidence and strength of recommendations. *BMJ* 2004;328(7454):1490.

(39) Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions. *http://www cochrane org/resources/handbook/Handbook4 2 6Sep2006 pdf* 2006. AccessedOctober 15, 2008.

(40) Jadad AR, Moore RA, Carroll D et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17(1):1-12.

(41) Maher CG, Sherrington C, Herbert RD, Moseley AM, Elkins M. Reliability of the PEDro scale for rating quality of randomized controlled trials. *Phys Ther* 2003;83(8):713-721.

(42) Reddy M, Gill SS, Kalkar SR, Wu W, Anderson PJ, Rochon PA. Treatment of pressure ulcers: a systematic review. *JAMA* 2008;300(22):2647-2662.

(43) Hinchliffe RJ, Valk GD, Apelqvist J et al. A systematic review of the effectiveness of interventions to enhance the healing of chronic ulcers of the foot in diabetes. *Diabetes Metab Res Rev* 2008;24 Suppl 1:S119-S144.

(44) Porta M. *A Dictionary of Epidemiology (5th Edition)*. New York: Oxford University Press; 2008.

(45) Peduzzi P, Henderson W, Hartigan P, Lavori P. Analysis of randomized controlled trials. *Epidemiol Rev* 2002;24(1):26-38.

(46) Altman DG, Schulz KF, Moher D et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med* 2001;134(8):663-694.

APPENDIX

An instrument to evaluate trials of the effectiveness of Negative Pressure Wound Therapy (NPWT).

Not all studies are equally credible. To assist in the process of deriving the "true" outcome of an intervention from conflicting studies it is common to award each of the studies a score reflecting its quality. However study designs vary greatly, depending on the type of intervention, and routine application of an unmodified quality measure may result in inappropriate quality scores. Furthermore, some quality evaluation tools (e.g. the CONSORT guidelines for randomized controlled trials[46] are designed to evaluate the quality of the report of the study rather than the credibility of its conclusions. We attempt here to outline an instrument appropriate for the evaluation of the credibility of randomized controlled studies on the effectiveness of Negative Pressure Wound Therapy (NPWT).

To develop this instrument, we referred to some well established instruments, the Cochrane[39], Jadad[40], the Physiotherapy Evidence Database (PEDro) scale[41], the Dutch Cochrane Collaboration Checklist[8]. Our instrument recognizes three principal sources of bias, selection bias, attrition bias, detection bias, and uncertainty due to sample size or unclear description of method. In particular we evaluated the method of randomization, the results of randomization, and baseline equality.

OBJECTIVE

The objective of the instrument is to assess**,** not the quality of the reports, but the credibility of the reported trials' outcomes**.** This is defined as "the likelihood of the trial design to generate unbiased results and approach the therapeutic truth" (Jadad) [40]. The instrument recognizes three principal sources of bias and one source of imprecision that diminishes the credibility of trial results

A. SELECTION BIAS

Selection bias can result from the use of an inappropriate method of randomisation, or from chance.

Randomization Method

Selection bias can occur when the method of randomization is inadequate, or when the result of randomization is inadequately blinded from the operator (e.g. random selection of the first case with subsequent alternation).

Points:

A1. Method of randomization **described** and **appropriate** …..0

A2. Method of randomization ***in*appropriate** …….. -1

A3. Method of randomization not adequately described ….....-1

Baseline Equality

Even when randomisation *methods* are adequate, imperfect randomisation may occur through chance. When this occurs it will cause inequality of baseline characteristics, defined here as a 5% or greater , clinically significant, uncorrected, difference between relevant baseline characteristics in the two arms of the study. Imperfect randomisation may be corrected by appropriate statistical adjustment, when the variables explaining the bias have been measured.

Points:

A4. There are no statistically uncorrected, clinically significant, differences between relevant baseline characteristics.....0

A5. There are uncorrected clinically significant baseline differences……..….-2

A6. It is unclear whether there has been adequate statistical correction for unequal baseline characteristics…….……....-1

B. DETECTION BIAS

The evaluator of the outcome should normally be blinded. In the case of wound healing this may be difficult or impossible. Failure to blind the measurement of ***objective*** outcomes, such as wound dimensions on photographs is less likely to lead to bias than failure to blind the

evaluation of ***subjective*** outcomes such as "state of wound healing" or "wound ready for graft ".

Points:

B1. Outcome evaluation has been blinded ……..…0

B2. There is unblinded evaluation of a *subjective* outcome .. -2

B3. There is unblinded evaluation of an *objective* outcome… -1

B4. Blinding of evaluation of outcomes is uncertain……..-1

C. ATTRITION BIAS

A dropout is "a person enrolled in the study who becomes inaccessible or ineligible for follow-up, e.g., because of inability or unwillingness to remain enrolled in the study" [44]. For present purposes we distinguish between dropouts and withdrawals. Withdrawals become inaccessible before treatment has been commenced.

Dropouts can cause bias by interfering with randomization. That dropouts are non-random may be evident from the given reasons, or from inequality of the numbers dropouts in the two arms of the study. The danger of bias will increase; if the difference in dropouts (%) is large between the two arms, if there is reason to believe they are non-random, and if there is reason to believe that the cause for the dropout is associated with the intervention or outcome.

In the presence of crossovers, or of dropouts for whom complete outcome data are available analysis should be by intention to treat (ITT). This normally means that "*all randomized subjects* are analyzed according to original treatment, and all events are counted against the assigned treatment". Peduzzi, 2002 [45]. For present purposes, we consider "modified intention-to-treat"(MITT) ,(meaning all randomized subjects *for whom treatment has commenced*) to be equivalent to ITT. ie: *withdrawals* of enrolled subjects that take place before an intervention has commenced are excluded from an ITT patient assignment.

In the absence of complete outcome information, there should be appropriate statistical adjustment for dropouts or crossovers.(e.g. survival analysis in studies recording time to event data or multiple imputation in studies that record outcomes only at the end of

the study). In the absence of such statistical adjustments the number of dropouts and their reasons (i.e. the probability they are not related to the intervention or outcome) influence the probability of bias. In this analysis, if the reasons given suggested the dropouts occurred at random, we considered that a Kaplan-Meier analysis would be an appropriate statistical analysis that made complete use of the available data.

Points:

When outcomes are arrived at through appropriate statistical analysis no points should be awarded for Section C. When the appropriate statistical analysis has not been used points should be scored as follows:

C1. Dropouts in either arm <5%……0
C2. Dropouts in either arm >4%, <15% ……-1
C3. Dropouts in either arm >14% ……-2
C4. Presence of dropouts unclear……-1
C5. Dropouts probably non-random *……..-2
C6. Reasons for dropouts not given……-1
C7. Analysis by Intention to treat……..…….……0
C8. Uncertain whether analysis is by Intention to treat…….-1
C9. Failure to analyze by intention to treat in the presence of dropouts /crossovers ……..-2

*** Non-random dropouts could be identified by the reasons given or by substantial (say>10%) inequality of dropouts in the two arms)**

D. SAMPLE SIZE AND STATISTICAL ANALYSIS

The study should be of sufficient size to provide both point estimates and standard deviation of the principle outcome.

Points:

D1. No statistical measurement of variability provided……. -1

or

D2. Sample size < 10 in either arm. ……...-1

SCORING SYSTEM

Subtract points from an initial score of ten.

Quality rating	**Points**
A (high)	9 or 10
B (moderate)	7 or 8
C (low)	6 or less